

## Response to the ACPA's Critique

The critique by Acquavella et al. (1) of the WRI report "Pesticides and the Immune System: The Public Health Risks" (2) represents significant progress, despite its criticisms. The pesticide industry now acknowledges that this issue is an important area for future research and evaluation. This position is very different from the pesticide industry's initial reactions to the report.

For the benefit of readers unfamiliar with this debate, we recapitulate the basic argument of the WRI report (2). It reviewed a large body of experimental research and wildlife studies, as well as the limited amount of human epidemiological research available on pesticide-induced dysregulation and suppression of the immune system. It found that, despite limitations in each of these areas of research, the body of evidence raises serious concerns regarding immunotoxicological consequences of pesticide exposure.

The report pointed out that if pesticides in common use do suppress immune responses, the public health risks could be serious, particularly in developing countries. In these regions, a large fraction of the population still lives in the countryside and works on farms. Pesticide use is increasing rapidly, and compounds that have long been banned or restricted on health grounds in the United States and Europe are still used. Health and safety regulations are weak and there is widespread evidence that farmworkers, their families, and others are significantly exposed. In addition, infectious and parasitic diseases are widespread, health care is inadequate, and for many in these populations, malnutrition has already compromised immune functioning. Additional weakening of immune defenses from pesticide exposure is difficult to detect because it manifests itself in heightened morbidity and mortality from common infectious diseases that are already among the leading causes of death.

The WRI report (2) recommended that immunological screening should be strengthened as part of the pesticide registration process, that an expanded international research program should be developed with emphasis on human epidemiological studies of vulnerable populations, and that steps should be taken to limit unnecessary exposures by improving training and regulatory programs, especially in developing countries. We continue to believe that these conclusions are fully justified by the available evidence.

The WRI report (2) referenced and briefly summarized nearly 200 experimental studies of pesticide immunotoxicity.

These studies varied widely in design, dose, exposure route, immunological biomarkers measured, and in presentation of results. Some studies developed dose-response relationships; others did not. Some reported measures of statistical significance for immunological deviations; others did not. However, most of those surveyed found evidence that major pesticide classes produced toxic effects on immune system organs, functioning, and competence.

Although the pesticide industry criticizes this body of evidence, many other scientists who have assessed the same literature reach similar conclusions (3). The WRI report (2) discusses, quotes from, and references these reviews. Of particular interest is the conclusion reached several years ago, on more limited evidence, by Dennis Flaherty (a co-author of the pesticide industry critique): "Pesticides should be considered presumptively immunotoxic from the limited animal and human data available and for the potential related to their widespread use" (4). We agree. Moreover, if pesticides are considered presumptively immunotoxic, doesn't it make sense to screen them more carefully, to step up research into human health impacts, and to reduce unnecessary exposures?

The WRI report (2) also examined the limited amount of human evidence available. We drew attention to ongoing Canadian research into an Inuit population exposed through diet to organochlorine compounds, including pesticide residues. The pesticide industry scientists question the relevance of this research but base their criticism on the wrong study (5). Following on that study, as the WRI report recounts, Eric Dewailly and his colleagues at the Laval University Hospital in Quebec initiated a prospective study of Inuit infants, examining chemical exposures, biomarkers of exposure, and clinical outcomes. Dewailly hypothesized that the high levels of organochlorines found in the typical Inuit diet were being passed in breast milk to infants, increasing their susceptibility to acute otitis media and other infectious diseases (6). Their study found decreased T-helper/T-suppressor cell ratios and increased incidence of acute otitis media associated with increased duration of breast-feeding and organochlorine levels in milk (5). It was also reported that exposed infants were hard to vaccinate because of insufficient antibody response to vaccines (8).

The pesticide industry critique mischaracterizes this important research, which implicates organochlorines in immune dysregulation and altered host resistance in a human population. Clearly, further research is warranted to sort out the role of

pesticides from that of other organochlorines and to resolve other issues (9).

The WRI report (2) refers to evidence that farmers and other groups exposed to pesticides experience higher risks of certain malignancies and suggests the possibility that reduced immune surveillance may promote these cancers. The pesticide industry critique (1) first questions whether cancer rates are affected by pesticide exposure. However, the National Cancer Institute has stated that exposure to the herbicide 2,4-dichlorophenoxyacetic acid or to certain organophosphate insecticides increases the risk of non-Hodgkin's lymphoma, particularly among farmers (10). The Institute of Medicine also states that there is sufficient evidence of an association between exposure to some herbicides and higher risks of non-Hodgkin's lymphoma, Hodgkin's disease, and soft-tissue sarcomas (11).

The pesticide industry critique (1) also questions whether pesticides increase susceptibility to cancers by weakening immune surveillance. Immune surveillance is a well-recognized component of host resistance to cancer. Exposures to such known immunosuppressive agents as cyclosporin A, a drug administered to transplant patients, results in strikingly increased risks of lymphatic tumors. Though evidence linking pesticide exposure to altered immune surveillance and cancer promotion is sparse, other experts, including an Italian Working Group on the Epidemiology of Hematolymphopoietic Malignancies, have also suggested the link (12). In a case-control study, Rothman et al. (13) found a strong dose-response relationship between polychlorinated biphenyl concentrations and risks of non-Hodgkin's lymphoma among a small sample of rural Americans, but only a nonsignificant positive association with concentrations of DDT residues. Ongoing studies in Italy should provide more evidence regarding an effect of pesticide exposure on immune surveillance (14).

The WRI study (2) identified epidemiological research literature on the immunotoxic effects of pesticide exposure on human populations extending back 20 years in the former Soviet Union. Because this literature was virtually unknown in the West, we provided references and summaries. It is appropriate that pesticide industry scientists have now examined this body of evidence. It is true that the studies would not meet currently accepted standards of epidemiological research. Most lack adequate controls on potentially confounding factors, adequate measures of exposure, or satisfactory control populations. Hence, the Soviet studies do not provide conclusive evidence of human

immunotoxic or health impacts. Nonetheless, they do show a pattern of immunotoxic effects consistent with the experimental evidence. The methodological weaknesses in these studies certainly do not exonerate pesticides as potential immunotoxicants. Rather, they emphasize the need for further properly designed epidemiological research, which is the conclusion the WRI report drew from them.

The WRI report (2) recommended that an expanded epidemiological research program be designed and organized, and we are happy that the pesticide industry has agreed to participate in an international expert meeting that will consider the serious issues involved in designing such research. We hope that this meeting will stimulate and enable a program of field research in exposed and vulnerable populations.

The WRI report (2) recommended that immunotoxicity testing of pesticides, as a condition of registration, be strengthened to reflect improved immunological methods, a need with which the pesticide industry concurred. We are happy that in the United States the EPA has announced increased testing requirements. However, these requirements will not be applied to pesticides already registered or reregistered. We hope that the pesticide industry will also voluntarily carry out this expanded battery of immunotoxicity tests on products already on the market.

It is evident that the conditions for safe use and disposal of pesticides are not now being met in much of the world. In view of the serious risks this poses to vulnerable populations, including the possibility of reduced resistance to widespread and often deadly communicable diseases, we hope that the pesticide industry will also cooperate actively in reducing unnecessary exposures.

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## Response

Repetto and Baliga have cast our critique, both implicitly and explicitly, as the work of vested interests and, therefore, of questionable merit. That is unfortunate. *Ad hominem* criticism is a barrier to the exchange of scientific views. Nonetheless, we hope readers will benefit from the time we spent to obtain, translate, and critically review the many foreign references cited in the World Resources Institute (WRI) report (1).

Our assessment of these references, contrary to the conclusion in the WRI report (1), is that we do not find credible evidence that modern, widely used pesticides are causing immune dysfunction in millions of people. The toxicologic studies cited in the WRI report have questionable relevance to real world exposure scenarios. The epidemiologic studies that were cited either have severe methodologic weaknesses or did not find an effect for pesticides. The studies of the Inuits deserve special mention. The ongoing dietary studies mentioned by Repetto and Baliga have not linked otitis media with dietary pesticide

exposure (2-4). These studies have focused on dioxins and polychlorinated biphenyls. Why imply that these studies (may) implicate pesticides? We made particular note of the study by Julien et al. (5) because it offered a plausible alternative hypothesis not mentioned in the WRI report: that the high prevalence of disease was associated with the change from a nomadic existence to a sedentary one. This explanation is consistent with the lesser disease prevalence among Cree Indians who share environmental factors with the Inuits.

Our assessment of the evidence does not mean that we oppose prudence in limiting pesticide exposure, that we oppose improvements in screening pesticides for possible immunologic effects, or that we oppose appropriate epidemiologic research. The admonition by Burrell, and our coauthor Flaherty, et al. (6)—published years before the WRI report—that "Pesticides should be considered presumptively immunotoxic...." reflects appropriate caution to minimize exposures to potential toxicants. Industry has been supportive of appropriate improvements in immunotoxic screening for pesticides, as evidenced by the collaboration of government and industry scientists to update EPA's Toxic Substances Control Act immunotoxicity testing guidelines. The related *Federal Register* notice (7) cites the work of many industrial immunotoxicologists.

Finally, we support improved epidemiologic research on potential immunotoxic effects of pesticides, but this is a difficult area in which to conduct research. Methodologic difficulties, as evidenced in past studies, must be recognized in order to make progress. Repetto and Baliga's characterization of our criticism notwithstanding, we hope our critique is helpful to scientists interested in this area of research.

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